Unitary Tract Infection Treatment

When to Use What Agents including Beta-lactam Combination Agents

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KEYWORDS

• Urinary tract infection • Pyelonephritis • Antimicrobial resistance

KEY POINTS

- Most cases of simple cystitis can be treated with oral antibiotics for short durations of therapy.
- Complicated urinary tract infections often require longer durations of therapy than simple cystitis.
- Multi-drug resistant organisms causing urinary tract infections are increasing.
- Newer antibiotics are available and effective for the treatment of urinary tract infections; however, they should be reserved for cases of drug resistance.

INTRODUCTION

One of the most common indications for antimicrobial use is urinary tract infection (UTI).[1] Despite this being one of the most common indications, there are still wide variations in practices when it comes to treatment.[1] If it is determined that a patient has UTI based on symptoms, and a decision is made to treat, multiple factors play a role in deciding on the most appropriate therapy including clinical classification and complexity of infection (complicated or uncomplicated), suspected pathogen and resistance risk, and patient-specific factors (eg, severity of illness, allergies, medication cost, co-morbidities).

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DISCUSSION

UTI is defined as a bacterial infection of the urinary tract.[2] One of the first steps to determine empiric antibiotics for treatment is to classify whether the patient has a complicated or uncomplicated infection. According the most recent Infectious Diseases Society of America (IDSA) guidelines, UTIs are considered complicated when there are signs or symptoms that suggest an infection extending beyond the bladder.[2,3] Complicated UTI (cUTI) includes catheter-associated UTI (CAUTI), bacteremic UTI, and UTI with fever or other evidence of systemic infection.[3] Patients with cUTI often have structural, functional, or metabolic conditions that promote infection and they are at increased likelihood of having an infection due resistant pathogens and treatment failure.[2–4] Other complicating factors include UTIs in the setting of chronic obstruction, nephrolithiasis, pregnancy, and immunosuppression.[3,5,6]

Uncomplicated UTI is a local bladder infection, without signs or symptoms suggesting infection extending beyond the bladder.[3,6] Symptoms typically include dysuria with or without frequency, urgency, suprapubic pain, or hematuria, and can occur in women or men.[2] Distinguishing between complicated and uncomplicated UTI is important in selecting empiric treatment to ensure adequate antimicrobial exposure at the site of infection.

When choosing an empiric treatment, potential pathogens and the risk for resistance should be considered. UTIs are primarily caused by Gram-negative pathogens, but Gram-positive pathogens may also be involved. In a study that included over 7000 isolates collected between 2012 and 2013 at multiple sites cross the United States in patients with UTIs, the most common organism isolated was *Escherichia coli* followed by *Klebsiella*, *Proteus,* and *Pseudomonas*.[7] The distribution of uropathogens may differ by type of infection or patient population.[8] Antibiotic resistance has steadily been increasing in *E. coli*. In the INFORM database that included 7272 isolates collected from 2012 to 2014 at 71 US medical centers, 10.6% of *E. coli* isolates were resistant to third-generation cephalosporins.[7] Incorporating the local antibiotic susceptibility patterns of suspected pathogen into the clinical decision process is critical in optimizing antibiotic selection. Other factors to consider with regards to resistance risk include past culture results, recent antibiotic use, recent hospitalization, and recent travel to areas with high rates of resistance.[1,9,10]

Approach to the Treatment of Uncomplicated Urinary Tract Infection

Uncomplicated UTI is a mild infection where narrow-spectrum oral antibiotics with low potential for collateral damage are preferred. The infection is often self-limited, even without treatment, and the risk of progression to tissue invasion or sepsis is minimal.[1]

Empiric antibiotics recommended for uncomplicated UTI include trimethoprim/sulfamethoxazole, nitrofurantoin monohydrate/macrocrystal or oral fosfomycin. Oral beta-lactams, fluoroquinolones and single-dose aminoglycosides may be considered as alternative treatment options.[1,11] When selecting an empiric antibiotic, clinicians should consider patient-specific factors (eg, allergies, cost, co-morbidities) and the risk of resistance to the targeted antibiotic. If resistance rates are high locally or there are risk factors present for resistance (**Fig. 1**), consider selecting an alternate agent.[1] Although urine cultures are often not obtained in the treatment of uncomplicated UTI, if they are obtained, therapy should be adjusted to incorporate the results of the urine cultures (particularly if the patient is not responding to empiric therapy), selecting an agent with activity against the identified pathogen but with also the narrowest spectrum.

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Specific Agents for the Treatment of Uncomplicated Urinary Tract Infection

Commonly used agents

Nitrofurantoin. Nitrofurantoin interferes with protein and DNA synthesis, impairing energy metabolism, cell wall, and carbohydrate synthesis.[12] It has activity against Gram-negative and some Gram-positive organisms including carbapenem-resistant *Enterobacterals* (CRE).[9] Nitrofurantoin achieves high urinary concentration (27%–50% of the drug is excreted unchanged in the urine) but does not penetrate well into the kidney parenchyma. Therefore, it should not be used for the treatment of pyelonephritis.[9] Randomized trials suggest high clinical cure rate with 5 to 7 day regimens, with minimal resistance promotion. One systematic review including 27 clinical trials utilizing nitrofurantoin for UTI showed clinical cure rates between 79% and 92% and low resistance rates of 0% to 5%.[13] Although older studies suggested that nitrofurantoin should be avoided in those with creatinine clearance less than 60 mL/minute, current data support efficacy in those with clearances of 30 mL/minute or greater.[12,14]

Trimethoprim–sulfamethoxazole. Trimethoprim/sulfamethoxazole works sequentially in inhibiting the production of folic acid. It possesses both tissue and urine exposure, and relatively broad Gram-negative activity, including *E. coli*.[14,15] A randomized, open-label trial comparing trimethoprim/sulfamethoxazole for 3 days and nitrofurantoin for 5 days, showed clinical cure of 79% in the trimethoprim/sulfamethoxazole group and 84% of the nitrofurantoin group (95% confidence interval, −13% to 4%).[16]

Oral fosfomycin. Fosfomycin trometamol has in vitro activity against *Enterobacterales* including extended spectrum beta-lactamase (ESBL)–producing isolates and *Enterococcus spp*. (regardless of vancomycin susceptibility) and works by interfering with cell wall synthesis of Gram-positive and Gram-negative bacteria.[17] In the United States, only oral fosfomycin is available. High urinary concentrations are achieved and concentrations in the renal parenchyma and serum are low.[14] IDSA guidelines recommend fosfomycin as first-line treatment for acute uncomplicated cystitis.[1]

In a meta-analysis of 27 clinical trials, fosfomycin had similar cure rates to fluoroquinolones, trimethoprim–sulfamethoxazole, or nitrofurantoin for cystitis in pregnant and nonpregnant patients.[18] However, an open-label, controlled trial of 513 women with uncomplicated cystitis found that 5 days of nitrofurantoin treatment resulted in greater clinical and microbiologic resolution at 28 days compared to fosfomycin (70% vs 58%; $P = .004$).[19] In addition, glucose-6-phosphate (G6P) is needed for fosfomycin to exert its bacterial killing,but this is not present in human urine. The minimum inhibitory concentrations determined in the presence of G6P may not accurately reflect the *in vivo* activity of the drug .[20] Due to these limitations, fosfomycin may be used for uncomplicated UTI but patients should be monitored closely for treatment response.

Alternative Antimicrobial Options

If any factors (such as allergies or concern for resistance) preclude use of the above first-line antimicrobials, oral beta-lactams are appropriate options. If beta-lactams cannot be used, fluoroquinolone or aminoglycosides are reasonable alternative options.

Beta-lactams. Beta-lactams, depending on the agent, have relatively broad Gram-negative and Gram-positive activity and work by inhibiting bacterial cell wall synthesis.[21] They are being used with increased frequency for UTI due to resistance to the first-line options.[14] Bioavailability and urine concentration varies per agent.[14] Beta-lactams have historically been considered second-line or third-line agents for

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uncomplicated UTI due to concerns pertaining to inferior efficacy based on older trials. However, treatment duration, selection of comparative antimicrobials, antibiotic dosing, definition of UTI, and clinical cure varied in these trials .[22] Sigurdsson and colleagues compared a 3 day regimen of amoxicillin therapy to a 3 day regimen of trimethoprim–sulfadiazine, and found amoxicillin to be less effective with regards to microbiological eradication; however, this study determined therapeutic efficacy according to bacteriologic findings.[23] The duration of beta-lactam antibiotic therapy in these trials may have been too short. Previous studies have shown beta-lactam antibiotics including amoxicillin and narrow-spectrum cephalosporins to be more effective when administered for at least 5 days compared to 3 days.[24] In a single-center retrospective chart review, short courses of cephalexin resulted in clinical success in greater than 80% of patients with uncomplicated UTI. In a multicenter randomized study comparing cefpodoxime–proxetil with trimethoprim–sulfamethoxazole in patients with uncomplicated cystitis, at 28 days after treatment, clinical cure (87.3% treated with cefpodoxime–proxetil vs 85% treated with trimethoprim–sulfamethoxazole) and bacteriologic eradication (86% treated with cefpodoxime–proxetil vs 84% treated with trimethoprim–sulfamethoxazole) were similar between groups.[25]

Amoxicillin and ampicillin are currently not recommended for empiric therapy because of the increased prevalence of resistance, but they may be prescribed for the treatment of UTIs when culture data show susceptibility, especially to *E. faecalis*. A review showed that even in the setting of *in vitro* resistance, amino penicillin concentrations in the urine may be high enough to achieve bacterial eradication and clinical cure for infections limited to the lower genitourinary tract.[26] A retrospective study evaluated outcomes of 84 adult patients hospitalized with ampicillin-resistant and vancomycin-resistant *Enterococcus*

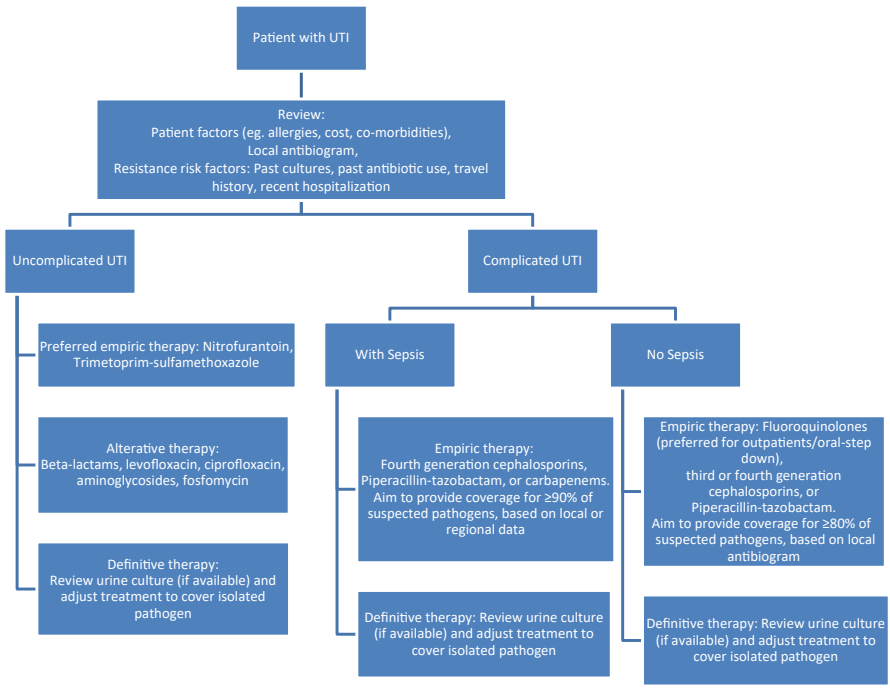

Fig. 1. Approach to the treatment of uncomplicated UTI.

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(VRE) isolates causing UTI who were treated with ampicillin. Treatment response was classified as clinical cure and microbiological eradication. Clinical cure was achieved in 88.1% of patients. Among those with follow-up cultures, microbiological eradication was achieved in 86% of patients.[27]

For uncomplicated cystitis, beta-lactams should be reserved as alternate agents due to their wider spectrum of activity compared to other first-line agents, but are often good options for those patients needing intravenous therapy. Common oral beta-lactams used for treatment of uncomplicated UTI include amoxicillin–clavulanate,[28] cefpodoxime,[25] and cephalexin.[22]

Fluoroquinolones (ciprofloxacin/levofloxacin). The fluoroquinolones inhibit DNA gyrase and partly bacterial topoisomerase IV.[29,30] These agents have favorable pharmacokinetic characteristics with high oral bioavailability (approximately 100% for levofloxacin), good tissue penetration and primarily renal elimination.[29,30] Among the fluoroquinolones indicated for the treatment of uncomplicated UTIs, both levofloxacin (85%) and ciprofloxacin (30%–50%) are predominantly excreted via the renal route, reaching very high concentrations in urine (521–771 and 200 mg/L, respectively).[14] Moxifloxacin attains lower urinary levels than other fluoroquinolones and should not be used to treat UTIs.[31] Fluoroquinolones are very effective for treatment of acute cystitis[28]; however, due to increasing resistance rates and adverse effects (eg, tendinitis, peripheral neuropathy, and central nervous system effects), they should be used only when options are limited and in select populations.[14]

Aminoglycosides. Aminoglycosides have broad aerobic Gram-negative activity, including resistant organisms and CRE, and work by inhibiting protein synthesis.[32] Aminoglycosides are excreted in high concentrations in the urine. As an example, following administration of only 1 mg/kg of gentamicin (well below the doses typically used for most gram-negative infections), peak urine concentrations may exceed 400 μg/mL. Additionally, after a single dose, concentrations remain above therapeutic levels for most uropathogens for 72 hours or longer.[33] Their clinical use has declined since the introduction of broad-spectrum antibiotics and due to concerns for aminoglycoside-associated nephrotoxicity.[34]

For the treatment of cystitis, a single dose of aminoglycosides can be used.[1] A systematic review assessing the efficacy of one-time parenteral aminoglycoside as UTI monotherapy included 13 studies. Cystitis was more common than pyelonephritis, and more females were represented than males. *E. coli* was the most commonly isolated uropathogen. The pooled microbiologic cure rate with single-dose aminoglycoside therapy was 94.5% ± 4.3%. Cure was sustained (ie, there was no recurrence) for 73.4% ± 9.6% of patients at day 30. Across all studies, 63 of 13,804 (0.5%) cases of nephrotoxicity, vestibular toxicity, or injection-site reaction were reported and no hearing loss was observed.[33] These data support aminoglycosides as a viable alternate regimen for patients with cystitis.

APPROACH TO THE TREATMENT OF COMPLICATED URINARY TRACT INFECTION

cUTI includes UTI in patients with complicating factors and systemic infection, including patients with febrile UTI, pyelonephritis, CAUTI, and bacteremic UTI.[3,14] Treatment efficacy is dependent on the delivery of antimicrobials in adequate concentrations to the site of infection (renal tissue, blood, or both), the drug should be active against the infecting organism and should have clinical efficacy for treatment.[35] Nitrofurantoin and oral fosfomycin do not attain adequate concentrations in the renal tissue or blood and thus should be avoided.[1]

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When selecting empiric treatment for patients with cUTI, the risk of resistance, local antibiogram, as well as patient-specific factors such as severity of illness, should be taken into account (see **Fig. 1**).[1,35] For those patients with risk factors for resistance to a preferred agent, consider selecting an alternate regimen. In those critically ill, septic patients, consider initiation of broader empiric antimicrobial coverage.[3] Recommended empiric agents include third-generation or fourth-generation cephalosporins, piperacillin–tazobactam, carbapenems (reserved for those patients with suspected multidrug-resistant (MDR) organisms including ESBL producers), levofloxacin (often reserved for outpatients), and ciprofloxacin (often reserved for outpatients).[3] When available, directed antimicrobial therapy, including oral step down therapy, should be guided by the results of urine culture and susceptibility testing. Patients who were initially treated with a parenteral regimen can be switched to an oral agent once they are hemodynamically stable, have adequate source control, and are able to take oral medications.[1,3] The selected oral agent should achieve adequate levels in urine, renal tissue, and in cases of bacteremia, in the blood, and should be active against the identified or likely causative pathogens.[1,3]

Specific Agents for the Treatment of Complicated Urinary Tract Infection

Beta-lactams

Beta-lactams are the backbone therapy for hospitalized patients with cUTI. For patients who are hospitalized and have no risk factors for infection with resistant organisms, initiating therapy with parenteral antibiotics that are likely to cover susceptible strains of the most likely pathogen *E. coli* such as ceftriaxone, is reasonable. For those patients with risk factors for resistant organisms, especially if critically ill, a broader antimicrobial targeted to cover these pathogens (such as cefepime, piperacillin–tazobactam, and carbapenems) should be initiated.[35] Oral beta-lactams may be used as initial therapy (particularly in ambulatory settings) as well as step-down therapy following initial parenteral therapy and/or as directed therapy.[1,35]

Fluoroquinolones (ciprofloxacin/levofloxacin)

For patients who have no contraindications to fluoroquinolones and are at low risk for fluoroquinolone resistance, oral fluoroquinolones may be considered for empiric therapy, particularly in the outpatient setting. If a patient's estimated likelihood of having a fluoroquinolone-resistant pathogen is 20% or greater, an alternate regimen should be considered. These agents may also be used as oral step-down therapy following parenteral therapy or as directed therapy.[1,35]

Aminoglycosides

The aminoglycosides are alternate treatment options for those patients unable to receive first line options, or as a parenteral lead-in treatment option or for patients at risk for or who have a history of MDR urinary pathogens.[1] Elbaz and colleagues conducted a cohort study comparing clinical outcomes with aminoglycosides versus other therapies for 2026 hospitalized patients with pyelonephritis. Death at 30 days occurred in 55 (7.6%) versus 145 (11%) patients treated with aminoglycosides and non-aminoglycosides, respectively (adjusted hazard ratio 0.78, $P = .013$). Median intravenous antibiotic duration was 4 days in both treatment groups.[34] Nephrotoxicity is the primary safety concern related to aminoglycoside use. In this cohort of patients treated according to a hospital protocol, the incidence of acute kidney injury was low (2.8%) and similar among patients treated with aminoglycosides and comparator antibiotics.[34] In addition, plazomicin, a new aminoglycoside with bactericidal activity against MDR including CRE, was non-inferior to meropenem in a randomized trial in patients with cUTI including pyelonephritis (composite cure 88.0% of the patients in

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the plazomicin group vs 91.4% in the meropenem group [95% confidence interval, −10.0 to 3.1]).[36]

Trimethoprim–sulfamethoxazole

Trimethoprim–sulfamethoxazole may be considered for treatment but due to high resistance rates should be reserved for instances when cultures indicate pathogen susceptibility to it, such as in cases of oral step-down therapy following parenteral therapy.[1]

Targeted treatment options

Although we ideally use narrow spectrum agents to treat UTIs, in situations where the organism is known to be or suspected of harboring antibiotic resistance, a broader spectrum agent that targets MDR is often required. Alternative agents include carbapenems and beta-lactam beta-lactamase inhibitors (BLIs). The agent of choice is dictated by the organism and susceptibility profile. Below are treatment options for specific resistant UTI pathogens.

Enterococcus

Linezolid and daptomycin both frequently retain activity against VRE infection in which nitrofurantoin and amoxicillin are not options. Linezolid has been shown to have similar outcomes compared to other agents for the treatment of mild UTIs although urinary excretion is approximately 30%.[37,38] Daptomycin, on the other hand, is approximately 50% excreted in the urine.[39] An open label trial comparing daptomycin to ciprofloxacin demonstrated similar efficacy in the treatment of UTIs due to Gram-positive organisms.[39] Case reports and case series evaluating daptomycin for the treatment of VRE UTIs have also shown promising results.[40–42]

MDR *Enterobacterales* including ESBL-producing *E. coli*, as well as other *Enterobacterales* have demonstrated increasing rates of resistance to first-line UTI therapies including trimethoprim–sulfamethoxazole and fluoroquinolones.[43–45] Some MDR *Enterobacterales* produce ESBLs. ESBLs consist of a group of enzymes that inactivate penicillin, cephalosporins, and aztreonam, and are most commonly produced by *Klebsiella spp*. and *E. coli*.[46] Although ESBL producers are frequently resistant to nitrofurantoin or trimethoprim–sulfamethoxazole, when *in vitro* activity is retained, these antibiotics remain viable options. In the case of resistance to these agents or if a patient is unable to take these medications due to allergies or intolerances, carbapenem antibiotics have historically been used to treat ESBL-producing *Enterobacterales*.[46]

The addition of BLIs to beta-lactam drugs help “broaden” the spectrum of activity against many Gram-negative organisms.[47] The BLIs work in synergy with beta-lactams against beta-lactamase-producing bacteria by preventing hydrolysis of the beta-lactam and restoring activity of the beta-lactam.[48]

Amoxicillin–clavulanate is an oral agent that extends the spectrum of amoxicillin with the addition of the BLI clavulanate.[49,50] It can be used for the treatment of UTIs including those caused by some strains of MDR *Enterobacterales*, although ESBL producers are often resistant. In a retrospective study evaluating the efficacy of amoxicillin–clavulanate for ESBL UTIs, the rate of cure was 84.7%.[51] The authors note that in isolates with higher MICs treatment failure was more common. Ampicillin–sulbactam is similar in spectrum of activity to amoxicillin–clavulanate but is available only in the intravenous formulation.

Piperacillin–tazobactam is a commonly used beta-lactam BLI with activity against Gram-positive and Gram-negative bacteria, including MDR *Enterobacterales* and *P.*

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aeruginosa. Multiple studies have evaluated piperacillin–tazobactam for the treatment of cUTIs and it has also been used as a common comparator agent versus newer beta-lactam beta-lactamase drugs.[52–54] A subset analysis of a clinical trial indicated numerically worse outcomes in patients with complicated ESBL-producing infections treated with piperacillin–tazobactam compared to a carbapenem.[55] For ESBL-producing infections, piperacillin–tazobactam might be effective for the treatment of simple cystitis; however, it is not recommended in more serious infections, such as pyelonephritis and sepsis.[46]

Carbapenem antibiotics

Ertapenem has been studied in the treatment of cUTIs due to both sensitive and ESBL-producing *Enterobacterales* and has demonstrated good efficacy.[56,57] Meropenem and imipenem–cilastatin have also been studied for the treatment of cUTIs and have been used as the comparator agent for clinical trials and have demonstrated good efficacy.[58,59]

Carbapenem-resistant Enterobacterales

Carbapenemases, including KPC, OXO-48, and NDM, are beta-lactamases that hydrolyze carbapenemase and are most commonly produced by *Enterobacterales*. Newer beta-lactams have activity against some of these carbapenemases and if the type of carbapenemase produced is known, then the choice of effective antibiotics can be more easily made (**Table 1**). In some instances, carbapenemase-producing organisms remain susceptible against agents such as trimethoprim–sulfamethoxazole, fluoroquinolones or nitrofurantoin, and in such instances, treatment with these agents is a viable option.

There are newer niche beta-lactam agents (most of which are beta-lactam beta-lactamase combinations) that have been approved for the treatment of cUTI infections. All those listed later are FDA approved for the treatment of cUTI except for sulbactam-durolobactam.

Ceftazidime–avibactam combines ceftazidime with avibactam, which is a diazabicyclo-octane inhibitor that is effective in inhibiting class A (eg, KPC), C (eg, ampC), and some D enzymes (eg, Oxa-48).[60] *In vitro* testing has revealed very potent activity against *Enterobacterales* with activity against over 99.9% of all isolates tested and 97.5% of carbapenem-resistant isolates.[61] A clinical trial comparing efficacy of ceftazidime–avibactam to doripenem for the treatment of cUTIs evaluated 810 patients.[62] Around 95% of patients grew an *Enterobacterales* and approximately 20% of all isolates were ceftazidime nonsusceptible. Investigator-determined clinical cure was equal in both arms (89.3%) and ceftazidime–avibactam met noninferiority endpoints compared to doripenem.

Meropenem–vaborbactam combines meropenem with vaborbactam, a boron-based BLI effective against class A enzymes.[63] When combined with meropenem, it restores activity against some *Enterobacterales*. *In vitro* testing has shown effectiveness against CRE that produce KPC enzymes, inhibiting 95.4% of such isolates tested.[64] In the TANGO I trial, patients with cUTI caused by known or suspected MDR organisms were treated with either meropenem–vaborbactam or piperacillin–tazobactam.[54] Of the 545 patients enrolled, there was overall success in 98.4% of the meropenem–vaborbactam group versus 94% in the piperacillin–tazobactam group.

Imipenem–relebactam combines imipenem with relebactam which is a bicyclic diazabicyclo-octane BLI which inhibits class A and class C enzymes. When combined with imipenem, this combination beta-lactam beta-lactamase has been shown to be effective for the treatment of cUTIs.[65] Imipenem–relebactam also has good activity

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Table 1
Overview of select beta-lactam antibiotics and common targeted pathogens

				Enterobacterales-producing					
Antibiotics	***Pseudomonas***	**Carbapenem-resistant *Pseudomonas***	***Enterobacterales***	**ESBL**	**OXA-48**	**KPC**	**NDM**	***Acinetobacter***	**Carbapenem-resistant *Acinetobacter***
Meropenem–vaborbactam	X		X	X		X			
Ceftazidime–avibactam	X	X	X	X	X	X			
Ceftolozane–tazobactam	X	X	X	X					
Imipenem–relebactam	X	X	X	X		X			
Cefiderocol	X	X	X	X	X	X	X	X	X
Sulbactam–durolobactam								X	X
Piperacillin–tazobactam	X		X						
Ampicillin–sulbactam			X					X	
Amoxicillin–clavulanate			X						

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against KPC-producing strains of CRE. *In vitro* data from US bloodstream isolates of CRE revealed 95% susceptibility to imipenem–relebactam.[66] Imipenem–relebactam is a viable treatment option for cUTI and pyelonephritis caused by susceptible strains of CRE.

Cefiderocol is a siderophore cephalosporin that is conjugated with a catechol moiety with a broad range of activity against Gram-negative bacilli.[67] Its mechanism of action with iron-binding transporters enhances its activity particularly against drug-resistant pathogens. *In vitro* testing showed higher efficacy of cefiderocol against many carbapenem-resistant organisms compared to the beta-lactam beta-lactamase combinations listed before.[68] Cefiderocol was effective for 89.2% of ceftazidime–avibactam-resistant isolates, 95.1% of meropenem–vaborbactam-resistant isolates, and 95.9% of imipenem–relebactam-resistant isolates.

In the APEKS–cUTI clinical trial comparing cefiderocol versus imipenem–cilastatin for cUTIs and pyelonephritis caused by Gram-negative pathogens that were not carbapenem resistant, cefiderocol was noninferior with primary efficacy endpoint at test of cure of 73% in the cefiderocol arm and 55% in the imipenem–cilastatin arm.[69] In the CREDIBLE-CR study, the investigators focused on infections due to carbapenem-resistant organisms and compared cefiderocol to best available therapy.[69] Of the 150 patients enrolled, 23 had cUTI. There was microbiological eradication in 9 of 17 (53%) patients in the cefiderocol group and 1 of 5 (20%) patients in the best available therapy group. Cefiderocol has excellent *in vitro* activity against resistant strains of *Enterobacterales* as well as *Pseudomonas*, but most published experience for cUTI has been with *Enterobacterales*.

Pseudomonas Including Carbapenem-Resistant Strains

P aeruginosa is a common hospital-acquired pathogen with limited oral antibiotic options and has the propensity for development of drug resistance via multiple mechanisms.[48] Treatment options consist of certain cephalosporins (ceftazidime, cefepime), piperacillin–tazobactam, aztreonam, quinolones (ciprofloxacin, levofloxacin), aminoglycosides (tobramycin, amikacin, plazomicin), and carbapenems (meropenem, imipenem–cilastatin).[48] It is important to note that gentamicin is no longer recommended for the treatment of *Pseudomonal* infections.[70]

Several of the more recently approved beta-lactam antibiotics have an indication for the treatment of cUTI and have enhanced activity against resistant strains of *P aeruginosa*. MDR *P aeruginosa* was listed as a serious threat in the CDC's antibiotic-resistant threats report in 2019.[71] Ceftolozane–tazobactam, ceftazidime–avibactam, and imipenem–relebactam are beta-lactam BLI combinations with *in vitro* activity against MDR isolates, including those that are carbapenem-resistant.[62,71,72] In a clinical trial comparing ceftolozone–tazobactam to levofloxacin in hospitalized patients for the treatment of cUTIs or pyelonephritis without known baseline pathogens, there was statistically significant higher composite cure rates in the ceftolozone–tazobactam arm compared to levofloxaxin (60% vs 39.3%).[62] However, only 12 of the 212 pathogens were *Pseudomonas* in the microbiological modified intention to treat population. In another retrospective analysis evaluating the use of ceftolozone–tazobactam for the treatment of MDR *Pseudomonas* infections, 28 of the 250 subjects had UTI with 89.3% having clinical success and microbiological cure.[73] In a prospective, randomized study comparing imipenem–cilastatin to imipenem–cilastatin with relebactam in patients with cUTIs, the clinical and microbiologic response rate was greater than 95% for both agents showing noninferiority. When evaluating specifically *Pseudomonas*, of the 230 isolates, 16 were *Pseudomonas* of which 31% were resistant to imipenem–cilastatin and 6% resistant to imipenem–relebactam.

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Another option for the treatment of serious infections due to MDR *Pseudomonas* including carbapenem-resistant strains is ceftazidime–avibactam. In vitro studies have shown that it is effective against 97% of all tested strains and 71.8% of strains that are nonsusceptible to first-line agents and carbapenems.[7] Another option for the treatment of MDR *Pseudomonas*, including carbapenem-resistant strains, is cefiderocol.[68] In an in vitro evaluation of over 2000 isolates, 256 were considered extensively drug-resistant of which 97.3% were susceptible to cefiderocol versus only 7.4% susceptible to meropenem.

Imipenem–relebactam is also a viable treatment option for resistant strains of *P. aeruginosa*. In the RESTOR-IMI trial, patients with serious infections due to imipenem nonsusceptible infections were randomized to receive either imipenem–relebactam versus imipenem plus colistin.[74] Approximately half of the 31 patients enrolled had a cUTI and the qualifying pathogen was *Pseudomonas* in 77% of the 31 patients enrolled. In this study, overall response for *P. aeruginosa* infections was noted in 13 of 16 patients in the imipenem–relebactam arm compared to 5 of 8 in the imipenem plus colistin arm. In addition, mortality and serious adverse events were lower in the imipenem–relebactam arm (10%) compared to in the imipenem and colistin arm (~30%).

Cefiderocol is also an option for the treatment resistant strains of *P. aeruginosa*. Although *in vitro* data are excellent, clinical experience with cefiderocol for the treatment of cUTI due to *P aeruginosa* is limited.

Carbapenem-resistant Acinetobacter baumannii

Sulbactam–durlobactam is the newest antibiotic in our armamentarium. Sulbactam has activity against *A. baumannii*, but resistance has been increasing, particularly among carbapenem-resistant strains. Durolobactam is a diazabicyclo-octane nonbeta-lactam, BLI with activity against classes A, C, and D carbapenemases which are often produced by carbapenem-resistant *A baumannii*. The treatment niche for sulbactam–durlobactam is for carbapenem-resistant *Acinetobacter* infections. The ATTACK trial evaluated sulbactam–durolobactam versus colistin, both administered with background imipenem cilastatin, for the treatment of ventilator-associated and hospital-acquired pneumonia.[75] It was shown to be noninferior and well tolerated in patients when combined with imipenem–cilastatin. It is excreted at high levels in the urine, and although not indicated for the treatment of urinary tract infection, might be an effective treatment option for cUTI due to carbapenem-resistant *A baumannii* when other options are not available.

SUMMARY

After confirming the presence of a true infection and need for antimicrobial therapy, the decision of which antimicrobial to use should be made with thoughtful consideration. First identifying the nature of the infection to be uncomplicated versus complicated and then risk factors for multi-drug resistance need be assessed. The goal of the prescribing provider is to choose the most appropriate and effective narrow spectrum agent when possible.

CLINICS CARE POINTS

- Many factors play a role in the choice of antibiotics for the treatment of UTIs, including but not limited to type of infection (uncomplicated vs complicated), severity of infection, known or suspected MDR organism, kidney function, allergies, and intolerances.

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- Use the narrowest spectrum antimicrobial based on available data—culture results from the patient including any available genetic resistance mutations or local rates of antibiotic resistance based on local or regional antibiograms.

DISCLOSURE

A. Yassin has no conflict of interest to disclose. T. Bhowmick served on the advisory board for Shionogi. K.S. Kaye serves as a consultant for Merck, Shionogi, Allecra, AbbVie, VenatorRx, Carb-X, Contrafect and Spero. He also participated on the advisory board for VenatoRx, DMID and Contrafact.

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